General Thoracic Surgery

Surgical treatment of primary lung cancer with synchronous brain metastases

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Objectives: The role of surgical resection for brain metastases from non–small cell lung cancer is evolving. Although resection of primary lung cancer and metachronous brain metastases is superior to other treatment modalities in prolonging survival and disease-free interval, resection of the primary non–small cell lung cancer and synchronous brain metastases is controversial.

Methods: From January 1975 to December 1997, 220 patients underwent surgical treatment for brain metastases from non–small cell lung cancer at our institution. Twenty-eight (12.7%) of these patients underwent surgical resection of synchronous brain metastases and the primary non–small cell lung cancer.

Results: The group comprised 18 men and 10 women. Median age was 57 years (range 35-71 years). Twenty-two (78.6%) patients had neurologic symptoms. Craniotomy was performed first in all 28 patients. Median time between craniotomy and thoracotomy was 14 days (range 4-840 days). Pneumonectomy was performed in 4 patients, bilobectomy in 4, lobectomy in 18, and wedge excision in 2. Postoperative complications developed in 6 (21.4%) patients. Cell type was adenocarcinoma in 11 patients, squamous cell carcinoma in 9, and large cell carcinoma in 8. After pulmonary resection, 17 patients had no evidence of lymph node metastases (N0), 5 had hilar metastases (N1), and 6 had mediastinal metastases (N2). Twenty-four (85.7%) patients received postoperative adjuvant therapy. Follow-up was complete in all patients for a median of 24 months (range 2-104 months). Median survival was 24 months (range 2-104). Survival at 1, 2, and 5 years was 64.3%, 54.0%, and 21.4%, respectively. The presence of thoracic lymph node metastases (N1 or N2) significantly affected 5-year survival (P = .001).

Conclusion: Although the overall survival for patients who have brain metastases from non–small cell lung cancer is poor, surgical resection may prove beneficial in a select group of patients with synchronous brain metastases and lung cancer without lymph node metastases.

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Lung cancer is the leading cause of cancer death in both men and women in the United States.[1] The incidence of brain metastases from lung cancer is approximately 40% to 60% in autopsy series.[2,3] Clinically, brain metastasis is diagnosed in 25% to 30% of patients with non–small cell lung cancer (NSCLC) during the course of their disease.[4,5] Surgical resection of these metastatic lesions is considered in only 25% of patients.[6] Several studies have reported long-term survival with surgical treatment of metachronous brain metastases in patients with primary NSCLC.[7,8] However, the results of surgical treatment of synchronous brain metastases along with the primary tumor is controversial. This review retrospectively examines our experience in patients who underwent resection of synchronous brain metastases and of the primary NSCLC and analyzes prognostic factors affecting survival.

Patients and Methods

From January 1975 to December 1997, 220 patients underwent surgical resection of brain metastases resulting from NSCLC at our institution. Twenty-eight (12.7%) of these patients underwent surgical resection of synchronous brain metastases along with the primary NSCLC. The medical records of these 28 patients were reviewed after we obtained institutional review board approval. The medical record of each patient was examined for age, sex, histologic type and grade, postoperative thoracic tumor stage, surgical procedure, postoperative complications, adjuvant therapy, and survival. Follow-up was obtained by outpatient visits and correspondence with primary physicians. Cerebral and pulmonary resection was considered curative if all gross evidence of disease was removed. In all patients, postoperative staging was done according to the 1997 International Staging System for Non–Small Cell Lung Cancer.[9] Operative mortality included patients who died within the first 30 days after the thoracic procedure and those who died later but during the same hospitalization. Survival was estimated by the Kaplan-Meier method with the date of diagnosis used as the starting point and the date of death or last follow-up as the end point.[10] The influence of variables on survival was analyzed by the log-rank test for multivariate analyses.[11,12]

Clinical Findings

The group comprised 18 men and 10 women. Median age was 57 years with a range of 35 to 71 years. Twenty-two (78.6%) patients had neurologic symptoms including headache in 9, ataxia in 7, seizure in 4, dizziness in 4, weakness in 3, vomiting in 2, and blurred vision and confusion in 1 each. Six patients had pulmonary symptoms, including chest pain in 2, hemoptysis in 2, and shortness of breath in 1. In 4 of the 28 patients, the location of the primary tumor was unknown at the time of initial presentation. Median time to the discovery of the primary tumor in these patients was 4 months with a range of 2 to 12 months. Preoperative workup included computed tomographic (CT) scanning of the chest and upper part of the abdomen, magnetic resonance imaging or CT scan of the brain, and bone scan.

Craniotomy preceded pulmonary resection in all 28 patients. A solitary brain metastasis was removed in 26 (92.9%) patients. Two patients had removal of 2 adjacent lesions in a single specimen. Cerebral resection was complete in all 28 patients. Median time between craniotomy and thoracotomy was 14 days with a range of 4 to 840 days. Pulmonary resection included pneumonectomy in 4 (14.3%) patients, bilobectomy in 4 (14.3%), lobectomy in 18 (64.3%), and wedge excision in 2 (7.1%). Wedge excisions were performed because of poor pulmonary reserve. Complete pulmonary resection and lymph node dissection was performed in all 28 patients. No patient had preoperative mediastinoscopy.

The tumor was adenocarcinoma in 11 (39.2%) patients, squamous cell carcinoma in 9 (32.1%), and large cell carcinoma in 8 (28.6%). The tumor was grade 2 in 1 patient, grade 3 in 6, and grade 4 in 21 patients. Lymph node metastases were present in 11 (39.3%) patients and were N1 in 5 (17.9%) and N2 in 6 (21.4%). For the lung tumor alone, the postoperative stage was stage IA or IB in 15 (53.6%) patients, stage IIA or IIB in 6 (21.4%), and stage IIIA in 7 (25.0%).

No patient received preoperative radiation or chemotherapy. Postoperative adjuvant therapy was given in 24 (85.7%) patients: whole brain radiation (WBR) alone in 15 (53.6%); WBR with systemic chemotherapy in 6 (21.4%); and WBR, systemic chemotherapy, and thoracic radiation in 3 (7.1%). The median dose of WBR was 35 Gy with a range of 25 to 40 Gy. Patients were selected to receive adjuvant therapy at the discretion of the surgeon and consulting oncologist or radiation therapist.

Results

There were no operative deaths after pulmonary resection. Complications occurred in 6 (21.4%) patients after the thoracic procedure and in 1 (3.6%) patient after the neurosurgical procedure. Vocal cord paralysis, empyema, pneumonia, atrial fibrillation, prolonged air leak, and postoperative bleeding necessitating reoperation occurred in 1 patient each after pulmonary resection. Only 1 patient had a complication, pseudomembranous colitis, after the neurosurgical procedure.

Follow-up was complete in all 28 patients for a median follow-up of 24 months and a range of 2 to 104 months. Recurrence developed in 18 (64.3%) patients and was local (5 lung, 3 brain) in 8 (44.4%), distant (2 bone, 2 adrenal, 1 adrenal/liver) in 5 (27.8%), and both local and distant (3 brain/lung, 1 brain/liver, 1 bone/liver) in 5 (27.8%). Four of the 7 (57.1%) patients who had cerebral recurrence did not receive adjuvant WBR. Three patients underwent late reoperation for recurrent brain metastases, 4 patients received thoracic radiation therapy, and 2 received chemotherapy for late distant recurrence. Currently, 4 patients are alive without evidence of recurrent disease at 10, 12, 39, and 49 months after pulmonary resection. The cause of death in the remainder was recurrent lung cancer in 18 (64.3%), unrelated to their cancer in 4 (14.3%), and unknown in 2 (7.1%).

Median survival was 24 months and ranged from 2 to

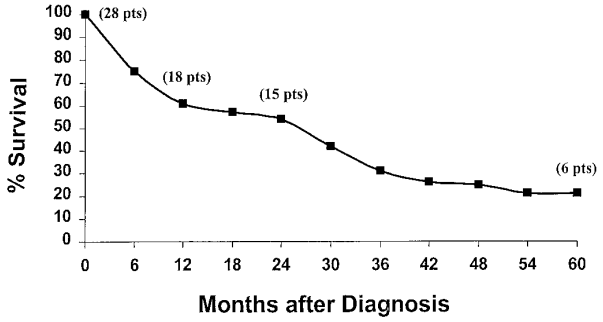

Figure 1. Probability of survival (death from any cause) of 28 patients who underwent resection of synchronous brain metastases and primary lung cancer. Zero time on the *abscissa* represents the date of diagnosis.

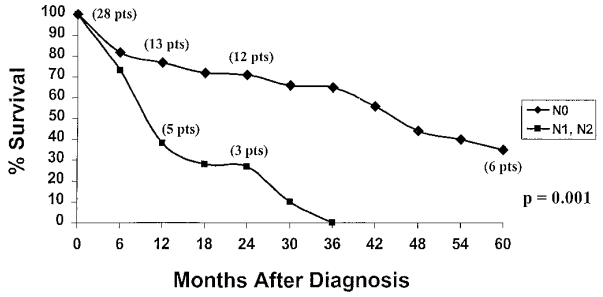

Figure 2. Probability of survival (death from any cause) of 28 patients who underwent resection of synchronous brain metastases and primary lung cancer, stratified by lymph node involvement. Zero time on the *abscissa* represents the date of diagnosis. Survival decreased with lymph node involvement (*P* = .001).

104 months. The overall survival at 1, 2, and 5 years was 64.3% (95% confidence intervals [CI], 48.8%-84.7%), 54.0% (95% CI, 37.9%-75.6%), and 21.4% (95% CI, 10.5%-43.6%), respectively (Figure 1). Lymph node metastases (N1 and N2) had a statistically significant impact on survival ($P = .001$). No patient with lymph node metastases survived longer than 3 years after resection (Figure 2). WBR affected survival, as median survival for patients who received WBR was 20.5 months compared with 4 months in patients who did not receive adjuvant WBR ($P = .18$). However, this difference was not significant. Adjuvant chemotherapy or thoracic radiation did not affect long-term survival.

Univariate analysis revealed that lymph node metastases and postoperative thoracic stage significantly affected survival. Multivariate analysis found that only lymph node metastases significantly affected 5-year survival. Age, sex, tumor histologic type or grade, primary tumor location, time interval between surgical procedures, type of resection, and adjuvant therapy did not significantly affect survival.

Comments

The development of brain metastases is usually a fatal event in the natural history of NSCLC. The median survival from the time of diagnosis of brain metastases to the time of death is approximately 1 to 2 months without treatment.[13] Corticosteroid administration in patients with brain metastases results in dramatic and rapid improvement in neurologic symptoms. However, corticosteroids do not prolong survival beyond 3 months.[14] WBR alone has early favorable results, with reduction of neurologic symptoms in more than 75% of patients. However, this benefit is short-lived, with a median survival of only 3 to 6 months.[15,16] In addition, the risk of dementia with high-dose WBR is significant.

Surgical resection of brain metastases from NSCLC has been performed for more than 70 years.[17] Early surgical resection of cerebral metastases was considered ineffective with rare long-term survivors because of inadequate neuroanesthesia techniques and perioperative care resulting in high morbidity and mortality.[18] With improved neurosurgical techniques and perioperative care, morbidity and mortality rates have decreased significantly. Resection of solitary brain metastasis has become standard treatment with low morbidity and an operative mortality of 0% to 3%.[19-21] There were no operative deaths in our report.

With these improved surgical outcomes, controversy developed as to which modality (surgery vs radiation therapy) should be used to treat patients with brain metastases from NSCLC. Two retrospective reviews compared WBR alone versus WBR plus surgical resection in patients with solitary NSCLC brain metastasis.[22,23] Both studies demonstrated a significant survival advantage of surgery plus WBR versus WBR alone. The median survivals of patients undergoing surgery and WBR was 16 to 19 months and only 4 to 6 months in patients receiving WBR alone. Two prospective studies randomized surgical resection plus WBR to WBR alone with similar results.[24,25] In addition, Patchell and colleagues[24] demonstrated that patients undergoing the combined approach also had significantly less recurrence at the original site of metastasis, as well as improved quality of life. The survival advantage of combined therapy found in the above reports was not evident in our report, but the trend was toward improved survival.

An alternative approach to cerebral resection is cerebral stereotactic radiosurgery (RS). RS delivers a single fraction of radiation to a specific intracranial target, thus minimizing exposure to the normal surrounding parenchyma. Retrospective studies of RS plus WBR for the treatment of brain metastases have demonstrated median survivals of 6 to 11 months.[26,27] Controversy exists whether WBR is of benefit when combined with RS. One nonrandomized study demonstrated that if WBR was not added to RS, local recur-

rence rates were higher but survival was not affected.[28] In contrast, a similar study demonstrated that WBR was of no benefit when combined with RS.[29] One retrospective report by Mehta and coworkers[30] analyzed patients who received WBR in combination with RS. In this study, the investigators observed a median survival of 13 months and improved functional independence and local control. These results were similar to those observed with surgical resection, suggesting that RS plus WBR is a reasonable alternative for patients with solitary brain metastasis or for patients with multiple metastases or surgically inaccessible lesions. Whether RS will be superior to surgical resection will require randomized prospective studies.

Patients in whom metachronous brain metastases develop from NSCLC have significantly improved survival after successful surgical resection with 5-year survivals of 21% to 45%.[19,20,31] Several factors have been found to influence survival, including complete resection, stage of tumor, locoregional disease, and prolonged interval between thoracotomy and craniotomy. Several reports have shown significantly worst survival with synchronous lesions.[32-34] Surgical resection alone for synchronous lesions resulted in 5-year survivals of only 5% to 10% with a median survival of less than 10 months.[32] Surgical resection of the primary lung tumor has been suggested to improve survival after craniotomy. Recently, Andrews, Gluck, and Konchingeri[33] demonstrated a median survival of 25.7 months in patients who underwent resection of the primary NSCLC compared with 9.1 months in patients who did not undergo resection of the primary tumor. Other reports of combined therapy also suggested improvement in survival, but the number of cases in each study was small.[35,36] Our report represents one of the largest series on the effectiveness of combined treatment of the primary tumor and synchronous brain lesions.

The most important determinant of survival in this report was the presence of lymph node metastases. Five-year survival of patients with N0 disease was 35%. No patient who had nodal involvement survived longer than 3 years after resection of the primary tumor. This is in contrast to the observations of Burt and associates,[37] who found no difference in survival between patients with stage I and II NSCLC versus patients with stage III and IV disease. However, they did demonstrate that patients who underwent complete resection had a significantly prolonged survival of 21 months versus 10 months for those who did not have resection or who had incomplete resection. All 28 of our patients had complete resection of their primary NSCLC.

This series represents a very select group of patients who underwent combined resection of stage IV NSCLC. Patients who have symptomatic synchronous brain lesions should undergo craniotomy first to prevent neurologic complications. Subsequent resection of the primary tumor should be performed only if there is no evidence of mediastinal lymph node involvement with mediastinoscopy. Complete resection of all disease should be performed. Operative mortality and morbidity for this combined approach is low. The majority of patients should receive adjuvant WBR.

In conclusion, resection of solitary synchronous brain metastases and the primary tumor should be performed only in a select group of patients with NSCLC. Preoperative evidence of mediastinal lymph node metastases should preclude resection of the primary tumor because long-term survival in those patients is poor.

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Discussion

Dr Joseph I. Miller, Jr *(Atlanta, Ga).* This topic presents a significant problem to thoracic surgeons, neurosurgeons, and oncologists alike. The authors have reported the second largest group of patients with synchronous brain metastasis, 28 of 220 patients, or 12.7% of their group during a 22-year period. The largest group reported was by Dr Michael Burt and his colleagues at Memorial before this society in 1991. At that time they reported on 65 patients, or 35% of their group, with synchronous brain metastasis during a 16-year period. Dr Magilligan from Detroit in 1988 reported on 14 patients with synchronous brain metastasis.

For metachronous single brain metastasis developing after resection of a primary lung cancer and in the absence of other metastatic disease, surgical resection of the cranial lesion followed by WBR is the treatment of choice. Therefore, my remarks will be confined to the subset of patients as addressed in this presentation.

The authors have correctly pointed out that the majority of these patients have neurologic symptoms and that craniotomy should be performed before thoracic resection. Twenty-four of their 28 patients received WBR at dosages from 2500 to 4000 Gy. Recurrent carcinoma developed in 18, and at present only 4 of the 28 are alive, at follow-ups ranging from 10 to 31 months. Seven had recurrence in the brain, of whom 4 had not received WBR. As reported by Dr Miller, the 1-year, 2-year, and 5-year survivals were 64%, 54%, and 21%, respectively.

No patient in the group with lymph node metastasis survived more than 3 years. The authors concluded that lymph node metastasis and WBR significantly influence survival. This is in contradistinction to findings of the Memorial group, who reported that surgical stage had no influence on long-term survival. This is also in contradistinction to the report of Magilligan in 1988 from Henry Ford Hospital, which showed no difference in long-term survival regardless of stage when a complete resection had been carried out. Magilligan's series was the third largest and received the Maxwell Chamberlain award at that time.

The authors point out that cerebrotactic RS may be an alternative to open craniotomy. Regardless, it appears that both groups benefit from WBR.

My own experience is limited to only 6 patients in the past 25 years with synchronous brain metastasis. Three of them had recurrent disease at 6 to 18 months, all intracranially, and 3 are alive at 1 year, 5 years, and more than 10 years, respectively. All patients received WBR.

I would like to ask the authors the following questions: First, how do you explain the discrepancy between the effect of pathologic stage of the lung cancer on survival in your study and the other 2 large reported series of Burt and Magilligan? Second, in your conclusions, you state that no patient with N1 or N2 disease determined preoperatively, excluding a positive mediastinoscopic result, should undergo resection. I think most surgeons might disagree with that. Third, which patients should undergo open cranial resection and which craniotactic RS? Does the decision depend on the surgeon's bias, and how does craniotactic RS affect outcome? Fourth, what is the current neurosurgical approach at the Mayo Clinic? Is it open or is it stereotactic surgery? Is WBR now given to all patients?

Dr Miller. Thank you, Dr Miller, for your comments and review of this paper.

To address your first question in regard to pathologic stage, you are correct that both Dr Burt's and Dr Magilligan's work demonstrated no significant survival change in regard to stage. There was a distinction in Dr Burt's paper in regard to complete and incomplete resection. We believe that with a larger patient population, ideally up to the numbers that Dr Burt generated at the Sloan-Kettering Cancer Center, stage might not prove to be significant..

As you recognized, only 11 patients in this population had stage II or stage III disease. We believe that complete resection of all gross disease neurosurgically and thoracically is the most important survival component.

In regard to our neurosurgical colleagues at the Mayo Clinic, they currently recommend open resection for patients who have a solitary brain metastasis from NSCLC. However, they are in the investigational stage of using RS. Furthermore, our colleagues at the Mayo Clinic published an article in the *Journal of Neurosurgery* in 1992, in which the use of WBR was discussed.

Currently all patients at the Mayo Clinic who undergo metastasectomy for NSCLC receive WBR.

Dr Mark J. Krasna *(Baltimore, Md).* I would like to discuss a paper presented by one of our group before the Southern Thoracic Surgical Association in 1997. The paper concerned 47 patients with synchronous metastasis and NSCLC. I bring it up because, in that group, we also found that there were no long-term survivors at 5 years with the N2 subgroup of patients; if the patients had N0 disease, the 5-year survival was 39%. I would reiterate all of your comments regarding the importance of lymph node staging.

I do have 2 questions similar to those asked earlier. We have used the Gamma Knife in lieu of craniotomy in our last 12 patients. What has changed, though, in our institution is that we are now accepting more than one metastasis. We are doing oligometastasectomies, if you will, by using 3 or 4 Gamma Knife lesions for brain metastases, not just solitary metastases. Is that being done as well at Mayo or are you just treating solitary brain metastases? Last, what would you do if you had a patient with no evidence of lymph node metastasis on CT scan but a solitary brain metastasis? Would you at the Mayo Clinic perform a mediastinoscopy now routinely before doing this operation?

Dr Thomas R. J. Todd *(Toronto, Ontario, Canada).* Mark, before he answers your question, I have a question for you. In your paper that was presented before the Southern Thoracic Surgical Association, do you recall within that group of 47 patients the number who had N2 disease?

Dr Krasna. It was at least half. I do not recall the exact number.

Dr Miller. At the Mayo Clinic, a patient who had a solitary brain metastasis would be treated by neurosurgical resection and then by mediastinoscopy after the recovery period. If the patient had evidence of mediastinal lymphadenopathy, we would not proceed with surgical resection for malignancy. That is why I concluded in our summary that in the future these patients may warrant systemic chemotherapy and thoracic radiation directed at the primary tumor, which may enable them to undergo surgical resection later. As you can see, this is very small number of patients, 28 patients over 27 years, so it would be very difficult to conduct a prospective study.

Dr Thomas W. Rice *(Cleveland, Ohio).* I would like to make a comment and ask 2 questions. We know that the prognosis for stage IIIA and IIIB lung cancer is dismal. Why should a metastasis to the brain make this more of a surgical disease? I always find that somewhat paradoxical.

The first question concerns the use of mediastinoscopy in the present group. Did you use mediastinoscopy routinely? From your other responses I would expect that you would now do mediastinoscopy in all these patients. Second, 72% of your patients had local recurrence, and I notice that you did not give any local therapy. What would your comments be on the management of a patient now when you perform resection regardless of the lymph node finding? Would you use radiation in the patients who otherwise have stage I and stage II disease?

Dr Miller. To answer your second question first, as Dr Miller mentioned, 4 of the 7 patients who had local recurrence within the brain did not undergo WBR; therefore, we would recommend WBR for all patients who underwent metastasectomy.

In regard to the chest, at the discretion of the oncologists and thoracic surgeons at that time, some of those patients did undergo systemic therapy afterward, but the decision was not based on nodal status.

In regard to mediastinoscopy, Dr Pairolero and Dr Trastek did the majority of these earlier cases, and mediastinoscopy was not performed routinely, but that policy has changed.

Dr Thomas M. Egan *(Chapel Hill, NC).* What will you do next week when you do a positron emission tomographic scan on one of these patients after the craniotomy and identify N1 disease? Will you operate or not?

Dr Miller. We do not have a positron emission tomographic scanner at the Mayo Clinic. If I had a patient with N1 disease at the present time, I would not recommend resection. I would recommend systemic chemotherapy and WBR.

Dr Thomas R. J. Todd. If I read your abstract correctly, this was a group of 28 patients out of 220 that came with synchronous brain and chest malignancy. What was different about those 28 that brought them to surgery?

Dr Miller. This was a select group that had only isolated cerebral metastasis.